Paper No. 23

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GORDON J. FREEMAN, VASSILIKI A. BOUSSIOTIS
and LEE M. NADLER

Appeal No. 2000-2063
Application No. 08/446,200

ON BRIEF[1]

Before ROBINSON, SCHEINER, and MILLS, Administrative Patent Judges.

ROBINSON, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 - 4, which are all of the claims pending in this application.

Claims 1 - 4 read as follows:

1. A method for selectively modulating a Th2-type response within a population of activated CD4+ T cells, comprising contacting the population of activated CD4+ T cells with an agent which modulates a B7-2 induced signal in the population of activated CD4+ T cells, such that the Th2-type response is modulated.

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[1] An oral hearing was scheduled on this appeal for December 13, 2001. Appellants waived the oral hearing on December 12, 2001 by fax communication. Therefore, we have considered this appeal On Brief.

2. The method of claim 1, wherein the Th2-type response is induced by contacting the population of activated CD4+ T cells with an agent which stimulates a B7-2 induced signal.

3. The method of claim 2, wherein the agent which stimulates a B7-2 induced signal in the population of activated CD4+ T cells is a stimulatory form of B7-2.

4. The method of claim 3, wherein the stimulatory form of B7-2 is a form of B7-2 which is attached to a solid phase support.

The references relied upon by the examiner are:

Linsley et al. (Linsley) 5,580,756 Dec. 3, 1996

Janeway et al. (Janeway) "Signals and Signs for Lymphocyte Responses," Cell, Vol. 76, pp. 275-285 (1994)

Hathcock et al. (Hathcock) "Comparative Analysis of B7-1 and B7-2 Costimulatory Ligands: Expression and Function," Journal of Experimental Medicine, Vol. 180, pp. 631-640 (1995)

Kuchroo et al. (Kuchroo) "B7-1 and B7-2 Costimulatory Molecules Activate Differentially the Th1/Th2 Developmental Pathways: Application to Autoimmune Disease Therapy," Cell, Vol. 80, pp. 707-718 (1995)

Ground of Rejection

Claims 1 - 4 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies upon Hathcock, Linsley, Kuchroo and Janeway.

We affirm this rejection for the reasons set forth herein.

Discussion

Grouping of the Claims

At page 4 of the Appeal Brief, appellants state that claims 1 - 4 do not stand or fall together. While appellants discuss the relationship of claims 2 - 4 to independent claim 1 (Brief, paragraph bridging pages 3-4), we find no arguments in the Brief which separately address the patentability of the dependent claims or any other indication why appellants regarded them as separately patentable over the prior art relied on by the examiner. 37 CFR § 1.192(c)(7) (1997) (Claims stand or fall together "unless a statement is included that claims the claims of the group do not stand or fall together and, in the argument under paragraph (c)(8) of this section, appellant explains why the claims of the group are believed to be separately patentable." (Emphasis added.)). Claims not separately argued stand or fall with those that are separately argued. In re Sernaker, 702 F.2d 989, 991, 217 USPQ 1,3, (Fed. Cir. 1983). Therefore, we have limited our consideration of the issues raised by this appeal to claim 1 as representative of all of the claims before us.

Claim Interpretation

Claim 1 is directed to a method for selectively modulating a Th2 response within a population of activated CD4+ T cells, comprising contacting the population of CD4+ T cells with an agent which modulates a B7-2-induced signal in the population of activated CD4+ T cells such that the Th2-type response is modulated. The Specification at page 5 states that "the Th2-type response" which is to be selectively

modulated includes a response by a subset of CD4+ T cells that is characterized by such features as production of the cytokines IL-4, IL-5, Il-10, and/or IL-13, as well as activation of basophils, mast cells, eosinophils, Ig isotype class switching, and stimulation of production of immunoglobulins, including IgG1 and IgE. However, we do not read the specification as limiting the Th2-response to those named in view of the use of the term "includes" which would suggest that other such responses, unnamed, would also be encompassed by this claim. The Specification (id.) further explains that "modulating" may include both stimulation and inhibition of a Th2-type response. At page 6, the Specification states that the phrase "a B7-2-induced signal" is intended to include, and thus is not limited to, a signal in the T cells that results from interaction of the B7-2 ligand on the T cell with a B7-2 molecule. The "agent" is stated to encompass any agent which modulates a signal in the T cell which naturally can be brought about by the interaction of B7-2 with a B7-2 ligand on the T cell and can include an agent which binds B7-2 to thereby inhibit interaction of B7-2 with its ligand or which binds the B7-2 ligand to trigger a B7-2 induced signal in the T cell. Such agents are stated to include stimulatory forms of B7-2 and other compounds, such as peptides, or small organic compounds which can act on the T cell to produce a signal that is normally induced by B7-2. However, it is clear that this language in the specification does not limit the nature of the agent which is encompassed by claim 1 to those specifically exemplified.

The rejection under 35 U.S.C. § 103

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the Examiner's Answer of July 19, 1999 (Paper No. 19) for the examiner's reasoning in support of the rejection and to the appellants' Appeal Brief filed May 7, 1999 (Paper No. 18) for the appellants' arguments thereagainst.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On the record before us, we find no error in the examiner's determination that the combined disclosures of Hathcock, Linsley, Kuchroo and Janeway are sufficient to establish a prima facie case of obviousness within the meaning of 35 U.S.C. § 103 as to the subject matter of claim 1.

The examiner relies on Hathcock as teaching (Answer, page 2):

> the expression, regulation and function of B7-2 and that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response (see entire document). For example, Hathcock et al. teach that in response to LPS or anti-IgD-dextran, murine B cells express B7-2 and at higher levels than B7-1 and that such quantitative differences in the amount of B7-1 and B7-2 expressed on activated B cells may profoundly influence their contribution to costimulatory function (Pages 634 and 638, in particular).

The examiner acknowledges that Hathcock does not "teach using immobilized B7-2 to stimulate activated T cells and induce their differentiation into Th2 cells." (Id.).

The examiner relies on Linsley as teaching (Answer, page 3):

> using soluble B7 including fragments and derivatives to stimulate T cells (see entire document). . . . [and] that B7 antigen is reacted with T cells in vitro to crosslink or aggregate the CD28 receptor, for example, using CHO cells expressing B7 antigen or immobilizing B7 on a solid substrate, to produce activated T cells (see column 12, lines 14-17, in particular). . . . [and] that T cells are activated with anti-CD3 and . . . [are] further stimulated with either a stimulating anti-CD28 antibody or soluble B7-Ig fusion protein.

The examiner cites Kuchroo as teaching that (id.):

> their data in experiments using anti-B7-1 and anti-B7-2 antibodies are direct evidence that interaction of the costimulatory molecules B7-1 on B7-2 with their counterreceptors CD28 and CTLA-4 on T helper precursors (Thp) during antigen presentation leads to polarization of Th responses and that the simplest interpretation of their data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (see entire document, particularly page 715, column 1, and Figure 7). Kuchroo et al. teach that the identification of intracellular signals that are generated by interaction of B7-1 and B7-2 with the same counterreceptors (CD28 and CTLA-4) on a Thp cell may provide insight into the molecular mechanisms responsible for Th cell differentiation, allowing selective manipulation of the immune response in disease (see page 715, last paragraph, in particular).

The examiner relies on Janeway as teaching (id.):

> that one of the most crucial events in the differentiation of naive CD4 T cells that respond to ligand presented together with costimulators is the decision whether to become a helper CD4 T cell (Th2), specialized for the activation of B cells to secrete antibody, or an inflammatory CD4 T cell (Th1), specialized to activate macrophages and stimulate cell-mediated immunity (see page 281, column 2, in particular). Janeway et al. teach that if the biochemical nature of differential signaling pathways are known, pharmacological agents can be developed capable of diverting T cell

> responses from harmful to innocuous by getting the T cell to reinterpret the signals it is receiving via its receptors.

The examiner concludes that (id.):

> one of ordinary skill in the art at the time the invention was made would have been motivated to stimulate CD3-activated T cells to differentiate to Th2 cells by activating them with immobilized soluble B7-2. One would have been motivated to substitute soluble B7-2 for B7 in the teachings of Linsley et al. because of Hathcock's teaching of B7-2 on activated B cells, Kuchroo's teaching that interaction with B7-2 induced activated T cells to differentiate to become Th2 cells, and Linsley's teaching that immobilized soluble B7 was very effective.

Thus, on this record, the examiner has provided evidence which would reasonably serve to establish that the claimed subject matter would have been prima facie obvious within the meaning of 35 U.S.C. § 103. Where, as here, a prima facie case of obviousness has been established, the burden of going forward shifts to the appellants. In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984), In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).

Appellants urge that the examiner has failed to establish a prima facie case of obviousness because the references, even taken in combination, fail to teach or suggest the claimed invention. (Brief, page 5). Appellants, initially, argue that Hathcock does not (Brief, page 6):

> teach or suggest ***modulating a Th-2 type response*** in a population of CD4+ T cells by contacting these cells with an agent which modulates a B7-2 induced signal. . . . [and] there is no teaching in Hathcock et al. relating to the Th-1 and Th2 pathways of maturation of CD4+ T cells, nor

> is there a teaching or suggestion relating to ***the differential role of B7-1 and B7-2 in these pathways***.

The examiner does not disagree with this analysis of Hathcock, but points out that Hathcock does "clearly teach the expression, regulation and function of B7-2 and that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response." We agree. Further, the perceived deficiencies of Hathcock are made up for by the remaining references.

With respect to Linsley, appellants argue that the reference does not make up for the deficiencies of Hathcock, fails to distinguish between the B7-1 and the B7-2 molecules and fails to provide the motivation to modulate the Th2-type responses by modulating the B7-2 induced signal as presently claimed. (Brief, page 7). The examiner does not find error in this interpretation of Linsley, but points out that Linsley does teach the use of immobilized soluble B7 molecules to stimulate T cells of interest in a manner to produce activated T cells. (Answer, page 4).

The appellants address the teachings of Kuchroo at page 8 of the Appeal Brief, urging that:

> Kuchroo et al. teach that CD4 T helper precursor cells mature along two alternative pathways (Th-1 and Th-2) and that these pathways are differentially activated by B7-1 and B7-2. Kuchroo et al. focus on the implications of this biological observation, in terms of susceptibility or resistance to a particular disease, but fail to teach or suggest a method for modulating a Th2-type response in a population of CD4+ T cells by contacting these cells with an agent with modulates a B7-2 induced signal. More importantly, Kuchroo *et al.* teach that an anti-B7-2 antibody

> ***enhances the production if INFλ*** (see page 708, first column, second paragraph), a cytokine known in the art and taught by Appellants to direct CD4+ T cells to differentiate into ***Th1 cells, not Th2 cells***. . . . In contrast, Appellants discovered that Th2 responses can be induced by stimulation of T cells with B7-2. Thus, . . . the ordinarily skilled artisan would have concluded that an agent which modulates a B7-2 induced signal in CD4+ T cells, would result in a Th1-type response not a Th2-type response.

To the extent that we understand appellants' arguments and interpretation of Kuchroo, we do not find the interpretation inconsistent with the examiner's reliance on this reference as discussed above. As we read Kuchroo a series of in vivo and in vitro studies were performed in order to examine:

> the role of the costimulatory molecules B7-1 and B7-2 in the differentiation of Thp cells to mature Th1 and Th2 effector cells and in the induction of an autoimmune disease, EAE. Utilizing MAbs specific for these two costimulatory molecules, we have shown that anti-B7-1 drives naive MBP-specific (myelin basic protein) Thp cells along a Th2 pathway while anti-B7-2 antibody favors Th1 development. (Page 713, column 2, Discussion).

The authors state that (Page 709, column 2, first full paragraph):

> [w]e then used this information to manipulate Th cell differentiation in vivo in EAE. To test the effect of anti-B7 antibodies on the development of EAE, we immunized SJL mice with various amounts of peptide (PLP(139-151) . . . In the first series of experiments, SJL mice were immunized with 50 µg of PLP(139-151) in CFA and injected every other day with 100 µg of anti-B7-1, anti B7-2, a mixture of anti-B7-1 plus anti-B7-2, or PBS. The antibody treatment was continued up to day 20.

The authors observed that (id.):

> Treatment with anti-B7-2 (2D10) alone did not have any ameliorating effect on disease. Similarly, treatment with a mixture of anti-B7-1 and anti-B7-2 had only a slight effect on delaying disease onset, and disease peaked on day 18 after immunization. The results from this initial experiment suggested that injection of anti-B7-1 alone had the most effect in ameliorating disease. The data further suggested that this was directed related to the antibody treatment, since stopping treatment on day 20 resulted in the appearance of disease in the remainder of the animals.

The authors, subsequently, state (Page 715, column 1):

> The simplest interpretation of our data is that B7-1 preferentially acts as a costimulator for generation of Th1 cells while B7-2 costimulates and induces Th2 cells (see model in Figure 7). Thus, blocking B7-1 will inhibit the generation of Th1 cells, while enhancing the generation of the Th2 cells and blocking B7-2 will have the opposite effect. If this hypothesis is correct, then the interaction of B7-1 and B7-2 molecules with their T cell counterreceptors likely generates different intracellular signals that lead to the differentiation of Thp cells along a Th1 or Th2 pathway.

It is not readily apparent how this teaching differs from appellants' discovery that Th2 responses can be modulated by controlling the interaction of the costimulatory antigen B7-2.

To the extent that appellants would urge that based on Kuchroo, "the ordinarily skilled artisan would have concluded that an agent which modulates a B7-2 induced signal in CD4+ T cells would result in a ***Th1-type response not a Th2-type response,***" it would appear that appellants are reading the appealed claims too narrowly. The claims do not explicitly require a stimulation of the Th2-type response, but require only that the Th2-type response be modulated. As we have interpreted claim 1, this could be either a stimulation or an inhibition of the Th2-response. (See Specification, page 5). The portion of Kuchroo to which appellants refer may well describe an inhibition of the Th2-type response resulting from the injection of a B7-2 antibody. However, this too would reasonably appear to fall within the scope of at least appealed claim 1.

The Kuchroo reference is of particular relevancy to the issue before us because it describes studies which would reasonably suggest that the individual costimulators

B7-1 and B7-2 are important in determining the differentiation of Thp cells to either Th1 or Th2 respectively. In the Discussion at page 713, column 2, to page 714, top of column 1, Kuchroo states:

> Administration of anti-B7-1 antibody [which would be expected to bind to and block the interaction of B7-1 with the relevant receptors] ameliorated an organ-specific autoimmune disease, EAE, whereas injection of anti-B7-2 antibody [which would have been expected to bind to and block the interaction of B7-2 with the relevant receptors] significantly worsened clinical and histological disease. . . . Our results further suggest that the ability of anti-B7 antibodies to inhibit or enhance EAE relates to the capacity of these antibodies differentially to activate Th1 or Th2 cells/cytokines upon contact with Thp cells in the peripheral lymphoid compartment. . . .In addition, we provide evidence that transfer of antigen-specific Th2 clones generated by blocking the B7-1 molecule can prevent an organ-specific autoimmune disease and can abrogate established disease.

Thus, Kuchroo provides the suggestion and motivation, which appellants found missing in both Hathcock and Linsley, to use an agent, such as the B7-2 described by Hathcock, to modulate and control the differentiation of activated CD4+ T cells to become Th2 cells which have been observed as being beneficial in the treatment or abrogation of immune disease.

The appellants, also, argue that Janeway may "teach the differentiation of naive CD4 T cells into either Th2 and Th1 cells," but fails "to teach or suggest a role for B7-1 and B7-2 molecules in this differentiation process." (Brief, page 9). However, as pointed out by the examiner, Janeway provides (Answer, page 5):

> further motivation at the time the invention was made to discern and characterize the nature of Th1/Th2 differentiation and, in turn, to apply this knowledge to pharmacological manipulations.

Appellants argue that (Brief, page 11):

> despite the fact that the prior art contained separate elements of the present invention, these individual teachings are insufficient to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention. It is Appellants' position that the motivation relied upon by the Examiner, which is not based on explicit suggestions within the cited references, but rather on what the Examiner argues that one of ordinary skill in this art would have known, is legally insufficient to establish the requisite suggestion to combine references.

We do not agree. We would note, initially, even if there was not an explicit suggestion to combine the teachings of these references, it is not necessary that the cited references or prior art specifically suggest making the combination. B.F. Goodrich Co. v. Aircraft Braking Sys. Co., 72 F.3d 1577, 1583, 37 USPQ2d 1314, 1319 (Fed. Cir. 1996) and In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988). Rather the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art. See In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991) and In re Keller, 642 F.2d 413, 425, 208 USPQ2d 871, 881 (CCPA 1981). Here, we agree, with the examiner, that the combined teaches of Hathcock, Linsley, Kuchroo, and Janeway would have suggested to one of ordinary skill in this art the likelihood that the one could have modulated the differentiation of activated CD4+ T cells in a manner, using agents available, including antibodies to B7-1 or B7-2, to direct the pathway of the Thp to either Th1 or Th2 as required by the present claims. Kuchroo, by describing the benefit of inhibiting or controlling certain immunological related disease conditions, provides both the

suggestion and the motivation to use this methodology to control or modulate the Th2 response.

To the extent that appellants urge that the examiner has failed to establish that one of ordinary skill in this art would have had a reasonable expectation of success of obtaining the claimed results, we would note that it is well established that a conclusion of obviousness need not be based upon absolute predictability. Rather only a reasonable expectation of success is needed to support a conclusion of obviousness. In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); In re Longi, 759 F.2d 887, 897, 225 USPQ2d 645, 651-52 (Fed. Cir. 1985). On this record, Kuchroo demonstrates that the Th-2 type response can be controlled or modulated in the manner presently claimed.

When considered anew, we find, on balance, that the arguments and evidence presented by the appellants, taken as a whole, fail to outweigh the evidence of obviousness provided by the examiner. Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988), cert. denied, 493 U.S. 814 (1989); and In re Beattie, 974 F.2d 1309, 1313, 24 USPQ2d 1040, 1043 (Fed. Cir. 1992). Thus, the examiner has established a prima facie case of obviousness within the meaning of 35 U.S.C. § 103, which appellants have not overcome either by arguments or convincing evidence. Therefore, we affirm the rejection of representative claim 1, and thus claims 2 - 4 under 35 U.S.C. § 103.

Other Issues

Having affirmed the rejection of all claims on appeal under 35 U.S.C. § 103, we find it unnecessary to raise a new rejection under 37 CFR § § 1.196(b). However, should further prosecution occur in this application, we would urge the examiner to step back and reconsider the relevance of Kuchroo as to at least appealed claims 1 and 2 in light of our interpretation of claim 1 as set forth above. It would reasonably appear from this record that both the examiner and appellants have focused their inquiry as to the patentability of the appealed claims on the use of B7-2 as the agent used to contact the activated CD4+ T cells. However, claims 1 and 2 are not so limited. In this circumstance, the claims should be given their broadest reasonable interpretation consistent with both the law and the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). When considered in this light, it would appear that both the examiner and appellants have not fully appreciated the relevance of Kuchroo.

As we have stated, Kuchroo describes studies which made use of antibodies to both B7-1 and B7-2 and observed the effective which resulted when these agents were brought into contact with activated CD4+ T cells, either in vivo or in vitro. It would reasonably appear that Kuchroo describes the modulation of the Th2-type response in a population of CD4+ T cells using an agent which modulates the B7-2-induced signal by contacting the CD4+ T cells with that agent wherein the agent is either an antibody to either B7-1 or B7-2. It is not readily apparent on this record why these described

embodiments would not be considered anticipatory of the subject matter of claims 1 and 2.

In the event of further prosecution, the examiner should review the Kuchroo article in light of the appropriate interpretation and if the examiner determines that there is a reasonable basis of questioning the patentability of any of the claim in the application on this basis, should issue an appropriate Office action explaining the reasoning in support of the conclusion reached and provide appellants with an appropriate opportunity to respond.

Summary

The rejection of claims 1 - 4 under 35 U.S.C. § 103 as unpatentable over the combination of Hathcock, Linsley, Kuchroo and Janeway is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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)
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